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| EXAMINER | |
|---|---|
| JUEDES, AMY E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/789,807 | TJOA ET AL. | |
| | Examiner | Art Unit | |
| | AMY E. JUEDES | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-29* is/are pending in the application.

4a) Of the above claim(s) *4-7,10-12,16 and 24-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 8-9, 13-15, and 17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 6/10/09 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/10/09 has been entered.

Claims 1 and 19-20 have been amended.

Claims 1 and 3-29 are pending.

Claims 4-7, 10-12, 16, and 24-29 stand withdrawn from further consideration pursuant to 37 CFR 1.14209 as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1, 3, 8-9, 13-15, and 17-23 are under examination.

2. The rejection of claims under 35. U.S.C. 102 as being anticipated by Bernard et al. is withdrawn in view of Applicant's amendment. Bernard et al. do not teach an immature dendritic cell having decreased expression of CD14.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 3, 8-9, 13-14, and 17-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Matera et al., 2000, in view of Bernard et al., 1998(of record).

As set forth previously, Matera et al. teach a method of differentiating dendritic cells comprising providing a population of peripheral blood monocytes that have been selected by magnetic sorting (i.e. non-activated), and contacting said monocytes with GM-CSF in the absence of additional cytokines (see page 30 and 31 in particular). Matera et al. also teach culturing in a serum free medium (see page 31 in particular). Matera et al. further teach that the dendritic cells generated by culture with GM-CSF express CD1a (see page 31 in particular). Additionally, the instant claims are drawn to a method of differentiating dendritic cells employing a dendritic cell precursor (i.e. a method of using a product made by a particular process). Thus, the method by which the monocytic precursor is produced does not carry patentable weight in the absence of a structurally difference (see MPEP 2113). The monocytic dendritic cell precursors of Matera et al. are the same as those produced by tangential flow filtration.

Matera et al. do not teach a low avidity culture vessel comprising PFTE.

Bernard et al. teach a method to generate dendritic cells from purified blood monocytes by culturing in a TEFLON$^{tm}$ (i.e. comprising PFTE) bag. Furthermore, Bernard teaches that said method meets good laboratory practice (GLP) procedures necessary for the clinical use of dendritic cells (see pg. 23).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the dendritic cells taught by Matera et al., using the TEFLON$^{tm}$ culture vessel, as taught by Bernard. The ordinary artisan at the time the invention was made would have been motivated to do so, since Bernard teaches that this method is useful for clinical purposes, since it involves the large scale differentiation of dendritic cells in a culture system that meets GLP procedures (see abstract and pg. 23). Moreover, one of ordinary skill in the art would have a reasonable expectation of success.

Applicant's arguments filed 6/10/09 have been fully considered, but they are not persuasive.

Applicant argues that Matera et al. disclose that the monocytes are selected by magnetic sorting with a CD14 specific antibody, and that as evidenced by Schutt et al., CD14 specific antibodies activates the monocytes. Thus, Applicant concludes that Matera does not teach a method directed to non-activated monocytic dendritic cell precursor differentiation.

The term "non-activated" is not specifically defined in the specification. Thus, "non-activated" cells might encompass a wide range of conditions. For example, a monocyte that is treated under conditions under which proliferation is not induced might

be considered “non-activated” (as is the case for a CD14 positively selected cell). Additionally, the instant specification discloses on page 10 that antibodies can be used to positively select for non-activated monocyte like cells that express CD14. Thus, based on the teachings of the specification, a "non-activated" monocyte encompasses those positively selected with anti-CD14 antibodies. Additionally, the resulting dendritic cells produced by the method of Matera et al. are identical to those of the instant claims (i.e. have decreased expression of CD14 and increased expression of CD1a, see page 31, in particular). Furthermore, Bernard et al. teach that monocytes can be isolated by aphaeresis (i.e. a "non-activating" method), and it would have been obvious to use aphaeresis as the method of monocyte isolating, since selecting among the various methods of monocyte isolating would involve choosing among a finite number of predictable options which could be pursued with a reasonable expectation of success. A person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense (see *KSR International Co. V. Telefex Inc* 82 USPQ2d 1385).

5. Claims 19-23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Matera et al. and Bernard et al., as applied to claims 1, 3, 8-9, 13-14, and 17-18 above, in further in view of Bosch et al., 2001 (of record).

As set forth previously, The teachings of Matera et al. and Bernard et al. are described above.

They not teach generating maturing the dendritic cells with IFN- and BCG.

Bosch teaches that dendritic cells can be matured with a combination of INF- and BCG (i.e. a bacterial antigen). Additionally, Bosch teaches that maturation with IFN- and BCG results in a dendritic cell population that can induce an immune response against a tumor antigen in cancer patients (i.e. a therapeutically useful dendritic cell population).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a dendritic cell, as taught by Matera et al. and Bernard et al., followed by maturation with BCG and IFN- as taught by Bosch. The ordinary artisan would have been motivated to do so, since Bosch teaches that IFN- and BCG are extremely potent maturation agents that result in a dendritic cell population that can induce an immune response against a tumor antigen in cancer patients (i.e. a therapeutically useful dendritic cell population). Moreover, one of ordinary skill in the art would have a reasonable expectation of success, since Bosch teaches the effectiveness of these techniques in the generation of dendritic cells.

Applicant's arguments filed 6/10/09 have been fully considered, but they are not persuasive.

Applicant argues that Bosch et al. do not remedy the defects of Matera et al. and Bernard et al. noted above.

However, Matera et al. and Bernard et al. do render the instant claims obvious for the reasons set forth above.

6. Claim 15 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Matera et al. and Bernard, as applied to claims 1, 3, 8-9, 13-14, and 17-18 above, and further in view of Lewalle et al., 2000 (of record).

As set forth previously, The teachings of Matera et al. and Bernard et al. are described above.

They do not teach using a cryopreserved cell population to generate dendritic cells.

Lewalle teaches the generation of dendritic cells from frozen peripheral blood mononuclear cells (see pg. 70). Furthermore, Lewalle teaches that many clinical protocols are based on sequential injections of dendritic cells, and therefore it would be of practical importance to have frozen aliquots of the same peripheral blood mononuclear cells for these purposes (see pg. 70).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the dendritic cell taught by Matera et al. and Bernard et al., using frozen peripheral blood mononuclear cells, as taught by Lewalle. The ordinary artisan at the time the invention was made would have been motivated to do so, since Lewalle teaches that many clinical protocols are based on sequential injections of dendritic cells (see pg. 70), and therefore it would be of practical importance to have frozen aliquots of the same peripheral blood mononuclear cells for these purposes. Furthermore, the ordinary artisan would have had a reasonable expectation of success, since Lewalle teaches that dendritic cells derived from frozen peripheral blood mononuclear cells retain their functional capacity (see pg. 73).

Applicant's arguments filed 6/10/09 have been fully considered, but they are not persuasive.

Applicant argues that Lewalle et al. do not remedy the defects of Matera et al. and Bernard et al. noted above.

However, Matera et al. and Bernard et al. do render the instant claims obvious for the reasons set forth above.

7. The following are new grounds of rejection.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 13-14, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated Matera et al., 2000.

Matera et al. teach a method of differentiating dendritic cells comprising providing a population of peripheral blood monocytes that have been selected by magnetic sorting (i.e. “non-activated" as disclosed on page 10 of the instant specification), and contacting said monocytes with GM-CSF in the absence of additional cytokines (see page 30 and 31 in particular). Matera et al. also teach culturing in a serum free medium (see page 31 in particular). Matera et al. further teach that the dendritic cells generated by culture with GM-CSF express increased CD1a and decreased CD14 (see page 31 in particular). Additionally, the instant claims are drawn to a method of differentiating dendritic cells employing a dendritic cell precursor (i.e. a method of using a product made by a particular process). Thus, the method by which the monocytic precursor is produced does not carry patentable weight in the absence of a structurally difference (see MPEP 2113). The monocytic dendritic cell precursors of Matera et al. are the same as those produced by tangential flow filtration. Furthermore, the culture conditions comprising culture with GM-CSF taught by Matera et al. can be considered "non-activating" since they do not result in the progression of a fully mature dendritic cells (see page 35, in particular).

Thus, the reference clearly anticipates the invention.

10. Claims 1, 14, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Kasinrerk et al., 1993.

Kasinrerk et al. teach a method of differentiating monocytes comprising providing a population of peripheral blood monocytes that have been selected by density centrifugation and negative selection (i.e. “non-activated"), and contacting said

monocytes with GM-CSF in the absence of additional cytokines (see page 581 in particular). Kasinrerk et al. further teach that the resulting cells have increased expression of CD1a (see page 581 in particular). Kasinrerk et al. also teach that the resulting cells have decreased expression of CD14 (see page 581 in particular). Thus Kasinrerk et al. describe a cell identical to that of the instant claims (i.e. the cells are immature dendritic cells). Furthermore, the culture of the monocytes with GM-CSF alone in the absence of other stimulating cytokines, as taught by Kasinrerk et al. can be considered “non-activating” conditions, as recited in the instant claims. Additionally, the instant claims are drawn to a method of differentiation comprising providing a "monocytic" cell population (i.e. a method of using a product (a monocyte) made by a particular process). Thus, the method by which the monocytic precursor is produced does not carry patentable weight in the absence of a structurally difference (see MPEP 2113). Although the monocytes of Kasinrerk et al. have been purified using a different process than tangential flow filtration, they nevertheless are structurally the same as the monocytic precursor cells of the instant claims.

Thus, the reference clearly anticipates the invention.

11. Claims 1, 3, 8-9, 13-14, and 17-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kasinrerk et al., 1993, in view of EP 0205387, 1986.

The teachings of Kasinrerk et al. are described above.

Kasinrerk et al. do not teach serum free medium, culturing in a low avidity culture vessel, and contacting the cells with an antigen, or with BCG and IFN-gamma.

EP 0205387 teaches a method for culturing monocytes in serum free medium in a low-avidity culture flask. EP 0205387 teaches using a TEFLON$^{TM}$ vessel (i.e. PFTE, see page 5 in particular). EP 0205387 teaches that the monocytes can be activated for therapeutic purposes by contacting the cells with antigen, or with compounds including IFN-gamma and BCG, see page 6-7 and 21, in particular). EP 0205387 teaches that the method provides precisely defined consistent and uniform conditions for obtaining large number of monocytes useful for experimental, pharmaceutical, or therapeutic purposes (see page 3, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the serum free low avidity culture system of EP 0205387, in the method of differentiating monocytes taught by Kasinrerk et al. The ordinary artisan would have been motivated to do so, since EP 0205387 teaches that that the method provides precisely defined consistent and uniform conditions for obtaining large number of monocytes useful for experimental, pharmaceutical, or therapeutic purposes. Additionally, it would have been obvious to further treat the differentiated monocytes of Kasinrerk et al., with antigen, BCG, and IFN-gamma, since IP 0205387 teaches that such treatments enhance activation of monocytes for therapeutic purposes.

12. Claims 1, 14-15, and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kasinrerk et al., 1993, in view of Stevenson et al., 1984.

The teachings of Kasinrerk et al. are described above.

Kasinrerk et al. do not teach a cryopreserved cell population.

Stevenson et al. teach that cryopreserved monocytes are suitable for culture. Stevenson et al. teach that the cyropreserved monocytes function similarly to fresh cells, and that they are more convenient and reproducible for use in vitro assays (see page 521, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the cryopreserved monocytes of Stevenson et al., in the method of differentiating monocytes taught by Kasinrerk et al. The ordinary artisan would have been motivated to do so, since Stevenson et al. teach that cyropreserved monocytes function similarly to fresh cells, and that they are more convenient and reproducible for use in vitro assays.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-

4471. The examiner can normally be reached on 7am to 3:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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